

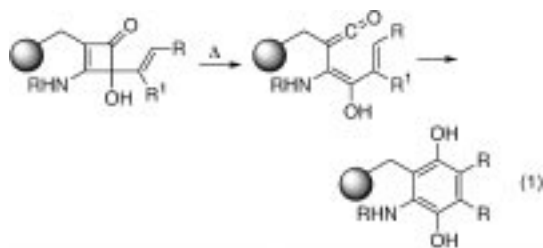
## Ketenes in Soluble Polymer Bound Synthesis: Preparation of Succinamides and 4-Pyridones

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Ketenes are versatile reactive intermediates,<sup>1</sup> but despite the great current interest in synthesis using polymer bound reagents<sup>2</sup> and reports of cumulenes attached to polymer supports for use as reactive reagents, including carbodiimides,<sup>3a–c</sup> isocyanates,<sup>3d</sup> diazoalkanes,<sup>3e</sup> and isothiocyanates,<sup>3f,g</sup> ketenes have received little attention in such reactions. In several instances ketenes<sup>4a–d</sup> or metal-complexed ketenes<sup>4e</sup> have reacted with polymer-bound reagents, and a cyclobutenedione-derived reagent attached to Wang resin has been shown to have many synthetic applications via ketene formation, including the preparation of quinone precursors (eq 1).<sup>4f</sup> The highly variegated reactivity of ketenes makes them attractive candidates for polymer bound reactions, and we now report two different applications of this approach, both utilizing poly(ethylene glycol) supports.<sup>2a</sup>

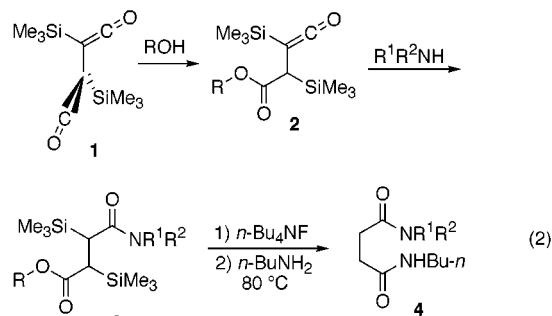


We have previously shown that the long-lived bisketene **1** is efficiently converted to ketenyl esters **2**<sup>5a,b</sup> and more recently have shown these may be converted to ester amides **3** (eq 2).<sup>5c</sup> To prepare a polymer bound ketene, monomethyl poly(ethylene glycol) ether (MPEGOH) with an average MW of 5000 g mol<sup>-1</sup> was reacted with **1** and Et<sub>3</sub>N, and the polymer was precipitated with Et<sub>2</sub>O and shown to contain the ketene by the IR band at 2086 cm<sup>-1</sup>. This is the first

Table 1. Yield and Purity of **4a–h**

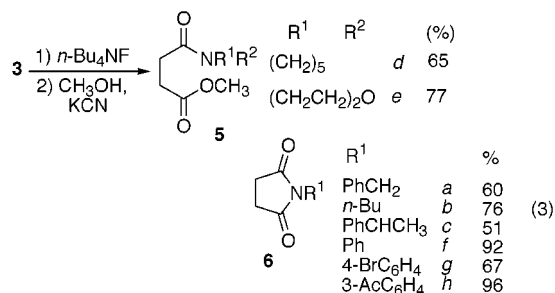
compd	R <sup>1</sup>	R <sup>2</sup>	yield (%)	purity (%)
<b>4a</b>	PhCH <sub>2</sub>	H	30	97
<b>4b</b>	<i>n</i> -Bu	H	66	84
<b>4c</b>	PhCHCH <sub>3</sub>	H	44	99
<b>4d</b>	(CH <sub>2</sub> ) <sub>5</sub>		38	88
<b>4e</b>	(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O		53	90
<b>4f</b>	Ph	H	71	99
<b>4g</b>	4-BrC <sub>6</sub> H <sub>4</sub>	H	59	99
<b>4h</b>	3-AcC <sub>6</sub> H <sub>4</sub>	H	62	98

reported ketene bound to a PEG support.<sup>6</sup> The <sup>1</sup>H NMR spectrum showed the formation of **2** (R = CH<sub>3</sub>OPEG) was complete, although there was evidently some desilylation adjacent to the ester function.



Reaction of **2** (R = CH<sub>3</sub>OPEG) with aliphatic primary and secondary amines to give amide **3** was quite rapid, while reaction with anilines took 3 days for completion. The <sup>1</sup>H NMR spectra showed amide formation was complete, but partial desilylation had occurred, and this was carried to completion by treatment with tetrabutylammonium fluoride (TBAF). Cleavage of the succinimide from the polymer with *n*-BuNH<sub>2</sub> gave the *N*-substituted *N*-*n*-butyl 1,4-butanamides **4**,<sup>7a</sup> which were obtained by simple filtration through silica gel, with purities assessed by HPLC and <sup>1</sup>H NMR (Table 1).

Desilylation and cleavage of **3** with CH<sub>3</sub>OH catalyzed by KCN<sup>8a</sup> gave ester amides **5** with the *N,N*-disubstituted



amides, while the monosubstituted amides gave succinim-

(6) For a polystyrene bound persistent ketene see: Liu, R., Ph.D. Thesis, University of Toronto, 1996.

(7) (a) These products were isolated and their own purity assessed by their <sup>1</sup>H NMR spectra, and new compounds were further characterized by <sup>13</sup>C NMR, IR, EIMS, and HRMS. (b) These products were isolated; their purity was assessed by their <sup>1</sup>H NMR spectra, and they were further characterized by IR and EIMS.

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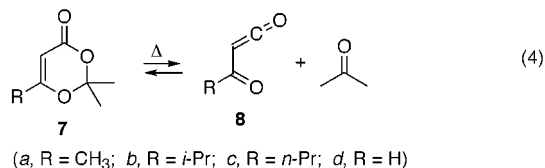
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ides **6**, with purities of 89–99% for **5d,e**, **6a,f–h** and 66% for **6c** as assessed by HPLC (eq 3).<sup>7a</sup>

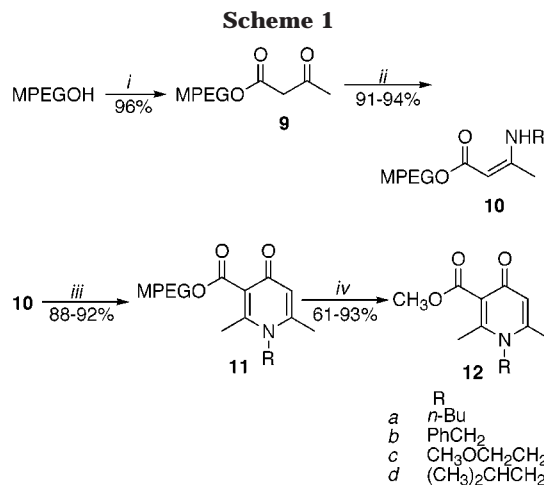
A second approach utilized the thermolysis of dioxinone **7a** to form acetylketene (**8a**) (eq 4)<sup>8b</sup> for use in cycloaddition reactions with polymer bound enamines. As shown in



Scheme 1 **7a** was also used for functionalization of MPEGOH, which was transformed to acetoacetate **9** by reaction with **7a** in refluxing toluene, and reaction<sup>8c,d</sup> with amines using trimethyl orthoformate gave enamines **10**. Reaction with **7a** in refluxing toluene gave the bound pyridones **11**. These were cleaved to the free pyridones **12** using KCN-catalyzed transesterification with CH<sub>3</sub>OH, and the MPEG was removed by filtration through silica gel giving the products in 91–98% purity as assessed by HPLC after evaporation of the solvent.<sup>7b</sup>

These procedures proved to be sensitive to the substitution pattern. Thus an amine with a secondary alkyl group (PhCHNH<sub>2</sub>CH<sub>3</sub>) gave the enamine **10**, but this did not react with **7a**, and acylketene precursors **7b–d** gave mixtures of products from which pyridones were not isolated.

In summary, the preparation and utilization of a polymer bound ketene **3** and the preparation of 4-pyridones through



*i*: **7a**, toluene, reflux, 5h; *ii*: RNH<sub>2</sub>, HC(OCH<sub>3</sub>)<sub>3</sub>, 24 h;  
*iii*: **7a**, toluene, reflux, 2h, repeat;  
*iv*: KCN, CH<sub>3</sub>OH, DMF, 60–70 °C, 60h

reaction of acetylketene **8a** with polymer bound enamines have been demonstrated.

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**Supporting Information Available:** Experimental procedures and NMR spectra (32 pages).

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